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EXPERT REVIEWS

Psychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: is there a link?

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Implantable cardioverter defibrillator (ICD) therapy is the first-line treatment for the prevention of sudden cardiac death. Despite the demonstrated survival benefits of the ICD, predicting which patients will die from a ventricular tachyarrhythmia remains a major challenge. So far, psychological factors have not been considered as potential risk markers that might enhance the prediction of sudden cardiac death. This article evaluates the evidence for a link between psychological vulnerability, ventricular tachyarrhythmias and mortality and the pathways that might explain such a link. This review demonstrates that there is cumulative evidence supporting a link between psychological vulnerability and risk of ventricular tachyarrhythmias and mortality in ICD patients independent of disease severity and other biomedical risk factors. It may be premature to include psychological factors in risk algorithms, but information on the psychological profile of the patient may help to optimize the management and care of these patients in clinical practice.

Keywords: arrhythmias • distress • implantable cardioverter defibrillator • mechanisms • mortality • psychological vulnerability

The implantable cardioverter defibrillator

Implantable cardioverter defibrillator (ICD) therapy constitutes state-of-the-art and first-line treatment for the prevention of sudden cardiac death (SCD) [1,2]. Key indications for ICD implantation are secondary prevention in patients who have survived a previous cardiac arrest without transient or reversible cause or spontaneous symptomatic sustained ventricular arrhythmia and primary prevention in patients who are considered at high risk due to a left ventricular ejection fraction ≤35% with ischemic or nonischemic cardiomyopathy in the absence of a history of cardiac arrest or sustained ventricular arrhythmia [3]. Risk reductions associated with ICD therapy compared with anti-arrhythmic drugs range from 37% for all-cause mortality to 57% for SCD, with ICDs being equally efficacious as primary and secondary prevention [4].

Arrhythmias affect the electrical system of the heart, producing abnormal heart rhythms that cause the heart to pump less effectively. The ICD continuously monitors the heart rhythm, and will provide the appropriate therapy (i.e., either antitachycardia pacing [ATP], cardioversion or a shock up to 800 V) to restore a normal rhythm if a life-threatening ventricular arrhythmia is detected. Generally, patients receive no warning prior to receiving a shock, and the shock itself may be uncomfortable and a disturbance to patients, who describe it as being similar to getting kicked in the chest by a horse [5].

The number of patients with heart disease living with a cardiovascular implantable electronic device (CIED), such as the ICD, a biventricular pacemaker providing cardiac resynchronization therapy (CRT) or a biventricular pacemaker with an ICD (CRT-D), has increased substantially [6,7]. Currently, nearly 1 million patients in North America and more than 800,000 in

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Europe have a CIED [8]. Since the approval by the US FDA and the first implantation in humans in 1980, the complexity of the ICDs has increased considerably with the introduction of novel features such as dual-chamber pacing and sensing, sophisticated algorithms to reduce the incidence of shocks and a 50-fold increase in device memory, while also reducing the size of the ICD (by a factor of 8) [9,10]. Hence, we are dealing with an increasing population of patients with an ICD with devices that are becoming increasingly complex, although more simple devices are now also being introduced, such as the entirely subcutaneous ICD system (S-ICD®; Cameron Health Inc., CA, USA), which is implanted without leads in or on the heart, thereby preserving the vasculature of the heart [11].

Risk stratification: an unresolved challenge

Despite the demonstrated benefits of ICD therapy, predicting which patients will die suddenly from a ventricular arrhythmia remains a major challenge in clinical cardiology practice. Left ventricular dysfunction has been used for risk stratification but appears to lack sufficient sensitivity and specificity to be a good predictor of risk for SCD [12]. Other potential candidates have been pursued, such as markers of autonomic nervous system functioning (e.g., heart rate variability and baroreflex sensitivity) and microvolt T-wave alternans, but as single markers, they seem to fall short of resolving the issue of optimal risk stratification [12]. Studies examining the contribution of multiple risk markers, such as the ABCD and the REFINE-ICD efficacy trials, show more promising results in terms of being closer to obtaining better prediction models [13,14]. The challenge of generating algorithms that are sufficiently sensitive and specific to predict which patients are at risk of SCD is probably attributable to the complex pathology underlying SCD and the contribution of several different processes and factors interacting, including markers of arrhythmic and nonarrhythmic death [12].

Risk stratification: is there a role for psychological factors?

The pursuit of factors that may help to enhance risk stratification has mainly focused on clinical factors and physiological markers, negating the potential role of psychological factors. At this point in time, it may be too premature to suggest the inclusion of psychological factors in risk algorithms. Nevertheless, there is evidence to suggest that traumatic and psychologically taxing life events, as shown in studies examining the impact of the terrorist attack on the World Trade Center on 9/11, may increase the risk of shocks in ICD patients with a relative risk of more than twofold [15,16]. Although such events are rare, psychological distress and morbidity are not uncommon in ICD patients with prevalence rates of approximately 20–25% for anxiety and depression, as reported in a recent meta-analysis [17]. Post-traumatic stress disorder (PTSD) is also seen in ICD patients, although the prevalence is somewhat lower, ranging from 7–11% [18,19]. Chronic levels of distress seem to be high in the subset of patients who are already anxious at the time of ICD implant, with as many as 50% of patients remaining anxious for 12 months postimplantation [20].

Whether distress in ICD patients should be attributed to the device itself, associated therapies such as appropriate and inappropriate shocks [21], hardware malfunctioning [22], underlying disease (e.g., symptomatic heart failure) [23,24], indication for ICD implantation [25], or the patient's preimplant psychological functioning [26] and personality disposition [27] is the subject of some debate. Irrespectively, if one out of four ICD patients suffers from significant levels of distress, there is a need to know whether this has consequences above and beyond its impact on quality of life [28] in this vulnerable subset of patients.

Hence, the aim of this review is to examine the evidence for a link between psychological vulnerability, ventricular tachyarrhythmias and mortality in ICD patients and to discuss the mechanisms that may be responsible for this link and the implications for future research and clinical practice.

Evidence for a link between psychological vulnerability & poor clinical outcome

To date, 15 individual studies have examined the association between psychological vulnerability and distress and ventricular tachyarrhythmias and mortality in ICD patients. Out of all studies, seven focused on ventricular tachyarrhythmias as the outcome, while six studies focused on mortality and two on both. Table 1 provides an overview of these studies, with the main results summarized in the following section.

Ventricular tachyarrhythmias

In 1999, Dunbar *et al.* were the first to examine the emotional status of the patient as a potential determinant of arrhythmias in ICD patients. A higher level of total mood disturbance, as assessed using the Profile of Mood States, was associated with a greater likelihood of experiencing an arrhythmia that required ATP, cardioversion or shock [29]. For each 10-point increase on the Profile of Mood States, the chance of experiencing an arrhythmia increased by 10–20%, after controlling for factors that are traditionally associated with arrhythmia risk. More specifically, higher anxiety, fatigue or confusion levels and a lower vigor level at 1- and 3-month postimplantation were associated with a higher risk of arrhythmia at 3 and 6 months, respectively. Neither anger nor depression was a significant predictor. Baseline level of mood disturbance before ICD implant did not predict occurrence of arrhythmic events at 1- or 3-month follow-up. In 2005, Whang *et al.* showed that moderate-to-severe depression (Center for Epidemiologic Studies Depression [CES-D] Scale ≥27) was associated with a statistically significant increased risk of appropriate ICD shocks, after controlling for multiple potential confounders [30]. However, three other studies in ICD recipients did not support an association between patient-reported health status [31], patient-reported [32] or physician-diagnosed [33] depression or anxiety and ventricular tachyarrhythmias. In two of these studies, the association between psychological distress and the occurrence of ICD shocks has approached statistical significance in univariate analysis ($p = 0.09$) [32,33].

Table 1. Studies examining the link between psychological factors, ventricular tachyarrhythmias and mortality.

Study (year)	n, mean age % men	Follow-up duration	Psychological factor(s)	Results of multivariable analyses (if available)	Covariates	Ref.
Ventricular arrhythmias (appropriate ICD therapy)						
Dunbar *et al.* (1999)	176 ICD patients 59.8 ± 13 years 82% men	1, 3, 6 and 9 months	Total Mood Disturbance (POMS) (10-point increase)	1 month: NS 1–3 months: OR: 1.16; 95% CI: 1.03–1.32; p = 0.01 3–6 months: OR: 1.14; 95% CI: 1.03–1.30; p = 0.04 6–9 months: NS	History of cardiac arrest, history of CAD, LVEF, amiodarone, β-blockers	[29]
Fries *et al.* (2002)	43 ICD patients presenting after appropriate shock 58 ± 13 years 81% men	N/A	Mental stress defined by the presence of negative emotions (tension/ nervousness, depression or anger) graded on a 4-point intensity scale during or up to a risk period of 1 h before arrhythmia recurrence	RR: 9.5; 95% CI: 6.3–14.5		[34]
Lampert *et al.* (2002) and Burg *et al.* (2004)	42 ICD patients that received one or more appropriate shocks 65 ± 7 years 78.6% men	N/A	Diary with a 5-point Likert Scale of intensity to evaluate levels of anger, anxiety, worry, sadness, happiness and feelings of challenge, interest and being in control (15 min preceding shock)	Anger: OR: 1.83; 95% CI: 1.04–3.16; p < 0.04 Anxiety: OR: 1.51; 95% CI: 0.93–2.42; p = 0.09 Worry: OR: 1.16; 95% CI: 0.72–1.84; p = 0.54 Sadness: OR: 1.22; 95% CI: 0.67–2.25; p = 0.52 Happiness: OR: 0.87; 95% CI: 0.60–1.25; p = 0.44 Challenge: OR: 1.24; 95% CI: 0.85–1.83; p = 0.27 Interest: OR: 1.02; 95% CI: 0.70–1.50; p = 0.92 In control: OR: 1.02; 95% CI: 0.67–1.56; p = 0.92	Multiple events within a single individual	[35,36]
Whang *et al.* (2005)	645 ICD patients (TOVA) 81.7% men	359 days (IQR 180–526)	Moderate-to-severe depression (CES-D ≥27)	First shock: HR: 3.2; 95% CI: 1.1–9.9. All shocks (including recurrent episodes): HR: 3.2; 95% CI: 1.2–8.6	Age, sex, number of prior ICD discharges, time from ICD implant to study enrollment, cardiac arrest as a device indication, CAD, angina class, NYHA class, LVEF, smoking, alcohol use, SSRI, ACE inhibitors, ARBs	[30]
Piotrowicz *et al.* (2007)	1058 patients ICD or CAU (MADIT-II) 84.1% men		Mental health (SF-12) Median cut-off - Per 10-unit decrease	HR: 1.28; 95% CI: 0.91–1.79; p = 0.16 HR: 1.10; 95% CI: 0.94–1.29; p = 0.24	Sex, NYHA class, presence of diabetes and BMI >30 kg/m^2	[31]

†The studies [39,40] both stem from the AVID trial, and they only differ in sample size, follow-up duration and covariates included.

ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BDI: Beck Depression Inventory; CABG: Coronary artery bypass graft surgery; CAD: Coronary artery disease; CAU: Care as usual; CES-D: Center for Epidemiologic Studies Depression Scale; CHF: Congestive heart failure; CRT(-D): Cardiac resynchronization therapy (with defibrillator); DS14: 14-Item Type D Scale; GMS: Global Mood Scale; HADS: Hospital Anxiety and Depression Scale; HR: Hazard ratio; ICD: Implantable cardioverter defibrillator; ICDC: ICD Concerns Questionnaire; IES-R: Impact of Event Scale – Revised; (LV)EF: (Left ventricular) ejection fraction; N/A: Not applicable; NS: Nonsignificant; NYHA: New York Heart Association; OR: Odds ratio; POMS: Profile of Mood States; PTSD: Post-traumatic stress disorder; QLI-CV: Quality of Life Index – Cardiac Version; QoL: Quality of life; SF-12/36: 12/36-Item Short Form Health Survey; SSRI: Selective serotonin reuptake inhibitor; STAI: State–Trait Anxiety Inventory; VT/VF: Ventricular tachycardia/fibrillation.

Table 1. Studies examining the link between psychological factors, ventricular tachyarrhythmias and mortality (cont.).

Study (year)	n, mean age % men	Follow-up duration	Psychological factor(s)	Results of multivariable analyses (if available)	Covariates	Ref.
Ventricular arrhythmias (appropriate ICD therapy) (cont.)						
Dougherty *et al.* (2009)	168 ICD secondary prevention 64.1 ± 12.3 76% men	12 months	Depression (CES-D ≥16) Anxiety (STAI ≥40)	OR: 1.01; p = 0.31 OR: 2.82; p = 0.09	—	[32]
Van den Broek *et al.* (2009)	391 ICD patients 62.3 ± 10.4 years 81% men	12 months	Depression (BDI ≥10) Anxiety (STAI ≥40) Type D personality (DS14)	NS NS NS Anxiety† Type D: HR: 1.72; 95% CI: 1.03–2.89; p = 0.04	Age, sex, ICD indication, etiology, LVEF, prolonged QRS duration, ACE inhibitors, β-blockers	[37]
Shalaby *et al.* (2012)	153 CRT-D patients 67.8 ± 10.5 years 98.7% men	31.4 ± 14.7 months	Diagnosis of mood disorder (anxiety, depression and/or PTSD)	6.1 ± 7.0 vs 3.3 ± 3.5; p = 0.09	Age, LVEF, etiology of cardiomyopathy, number of shocks, smoking, echocardiographic improvement	[33]
Mortality (all-cause)						
Piotrowicz *et al.* (2007)	1058 patients ICD or CAU (MADIT-II) 84.1% men	3 years	Mental health (SF-12) Median cut-off Per 10-unit decrease	HR: 1.39; 95% CI: 1.00–1.93; p = 0.05 HR: 1.21; 95% CI: 1.04–1.42; p = 0.02	Age, sex, EF, CHF, NYHA class, blood urea nitrogen level, resting heart rate, treatment group	[31]
Ladwig *et al.* (2008)	147 ICD patients (LICAD) 85% men	5.1 ± 2.2 years	PTSD (upper quartile IES-R)	HR: 3.45; 95% CI: 1.57–7.60; p = 0.002	Age, sex, survey, LVEF, CAD diagnosis, prior resuscitation, β-blockers, number of ICD shocks, time since ICD implantation, depression, anxiety, comorbidities	[41]
Steinberg *et al.* (2008)†	740 patients with ICD or antiarrhythmia (AVID) 64 ± 10 years 82% men	1.5 ± 10 years	Mental health (SF-36) 46-item Patient Concerns Checklist Disease-specific QoL (QLI-CV)	NS HR: 1.03; p = 0.01 (survival) HR: 0.95; p = 0.02 (survival)	Age, sex, race, index arrhythmia type (VT/VF), CHF, LVEF, β-blockers, therapy group	[40]

†The studies [39,40] both stem from the AVID trial, and they only differ in sample size, follow-up duration and covariates included.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BDI: Beck Depression Inventory; CABG: Coronary artery bypass graft surgery; CAD: Coronary artery disease; CAU: Care as usual; CES-D: Center for Epidemiologic Studies Depression Scale; CHF: Congestive heart failure; CRT(-D): Cardiac resynchronization therapy (with defibrillator); DS14: 14-Item Type D Scale; GMS: Global Mood Scale; HADS: Hospital Anxiety and Depression Scale; HR: Hazard ratio; ICD: Implantable cardioverter defibrillator; ICDC: ICD Concerns Questionnaire; IES-R: Impact of Event Scale – Revised; (LV)EF: (Left ventricular) ejection fraction; N/A: Not applicable; NS: Nonsignificant; NYHA: New York Heart Association; OR: Odds ratio; POMS: Profile of Mood States; PTSD: Post-traumatic stress disorder; QLI-CV: Quality of Life Index – Cardiac Version; QoL: Quality of life; SF-12/36: 12/36-Item Short Form Health Survey; SSRI: Selective serotonin reuptake inhibitor; STAI: State–Trait Anxiety Inventory; VT/VF: Ventricular tachycardia/fibrillation.

Table 1. Studies examining the link between psychological factors, ventricular tachyarrhythmias and mortality (cont.).

Study (year)	n, mean age % men	Follow-up duration	Psychological factor(s)	Results of multivariable analyses (if available)	Covariates	Ref.
Mortality (all-cause) (cont.)						
Kao *et al.* (2010)†	507 patients ICD or antiarrhythmia (AVID) 64.85 ± 10.81 years 78.3% men	12 months	Mental health (SF-36) Disease-specific QoL (QLI-CV)	OR: 1.23; 95% CI: 0.82–1.85, p = 0.32 OR: 0.48; 95% CI: 0.23–0.99, p = 0.05	Age, race, LVEF, NYHA, history of CHF, history of hypertension, hyperlipidemia and CABG, β-blockers, diuretics, ACE inhibitors, lipid-lowering medication	[39]
Pedersen *et al.* (2010)	371 ICD patients (MIDAS) 57.7 ± 12.0 years 79.5% men	1.7 ± 0.5 years	Type D personality High device-related concerns (ICDC ≥13)	HR: 2.79; 95% CI: 1.25–6.21, p = 0.01 HR: 2.38; 95% CI: 1.06–5.34, p = 0.04 Type D† high concerns: HR: 3.86; 95% CI: 1.64–9.10; p = 0.002	Age, sex, ICD indication, etiology, shocks	[42]
Van den Broek *et al.* (2011)	591 ICD patients 62.7 ± 10.1 years 80.7% men	1150 days (281–2384 days)	Negative mood (GMS) Positive mood (GMS) Depression somatic symptoms (BDI) Depression cognitive symptoms (BDI)	HR: 1.03; 95% CI: 1.01–1.06; p = 0.002 HR: 1.01; 95% CI: 0.98–1.03; p = 0.61 HR: 1.13; 95% CI: 1.04–2.23; p = 0.003 HR: 0.97; 95% CI: 0.91–1.03; p = 0.29	Age, sex, relationship, indication, CAD, CRT, LVEF, diabetes, smoking, β-blockers, ACE inhibitors, shocks	[37]
Tzeis *et al.* (2011)	236 ICD patients (LICAD) 58.6 ± 14.0 years 77.8% men	6.1 ± 2.5 years	Depression (HADS ≥ 8)	NS	Age, sex, ischemic cardiomyopathy, LVEF, NYHA, shocks, diabetes, renal failure, β-blockers, survey employed	[43]
Shalaby *et al.* (2012)	153 CRT-D patients 67.8 ± 10.5 years 98.7% men	31.4 ± 14.7 months	Diagnosis of mood disorder (anxiety, depression and/or PTSD)	NS	Age, LVEF, etiology of cardiomyopathy, number of shocks, smoking, echocardiographic improvement	[33]

†The studies [39,40] both stem from the AVID trial, and they only differ in sample size, follow-up duration and covariates included.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BDI: Beck Depression Inventory; CABG: Coronary artery bypass graft surgery; CAD: Coronary artery disease; CAU: Care as usual; CES-D: Center for Epidemiologic Studies Depression Scale; CHF: Congestive heart failure; CRT(-D): Cardiac resynchronization therapy (with defibrillator); DS14: 14-Item Type D Scale; GMS: Global Mood Scale; HADS: Hospital Anxiety and Depression Scale; HR: Hazard ratio; ICD: Implantable cardioverter defibrillator; ICDC: ICD Concerns Questionnaire; IES-R: Impact of Event Scale – Revised; (LV)EF: (Left ventricular) ejection fraction; N/A: Not applicable; NS: Nonsignificant; NYHA: New York Heart Association; OR: Odds ratio; POMS: Profile of Mood States; PTSD: Post-traumatic stress disorder; QLI-CV: Quality of Life Index – Cardiac Version; QoL: Quality of life; SF-12/36: 12/36-Item Short Form Health Survey; SSRI: Selective serotonin reuptake inhibitor; STAI: State–Trait Anxiety Inventory; VT/VF: Ventricular tachycardia/fibrillation.

Three studies examined the link between psychological distress and ventricular arrhythmias in ICD patients that had already received one or more shocks. Using structured interviews, Fries *et al.* asked patients who had received an appropriate shock to indicate the presence and intensity of negative emotions (i.e., tension/nervousness, depression or anger) during 1 h before a recurrent shock [34]. Based on the responses, the calculated relative risk of arrhythmia recurrence associated with mental stress was 9.5 (95% CI: 6.3–14.5). In another study, 42 ICD patients were asked to complete a diary page when they experienced a shock to retrospectively evaluate their mood state in the 15 min preceding the shock [35]. Results showed that moderate levels of anger were more likely during the period preceding shock than during a matched control period 1 week later. Other mood states (i.e., anxiety, worry, sadness, happiness, challenge, feeling in control or interest) did not differ prior to shock compared with the control period. In 2004, Burg *et al.* showed that the patients in this sample who reported at least moderate anger in the 15 min preceding shocks scored significantly higher on trait anger than those who did not ($p < 0.0001$) [36]. Trait anger was independently associated with anger-triggered arrhythmias ($p < 0.0001$). In addition, patients who reported at least moderate anxiety before shock scored significantly higher on trait anxiety ($p < 0.008$). Van den Broek *et al.* showed that the clustering of anxiety at the time of implant and having a distressed (Type D) personality predicted arrhythmia, while no main effect was found for anxiety or depression [37]. Patients with a Type D personality experience a broad range of negative emotions and tend to inhibit self-expression in social interaction [38]. The two latter studies suggest that stable psychological factors increase the risk of emotion-triggered appropriate shocks in ICD patients.

In aggregate, there is some evidence that psychological distress may increase the risk for ventricular arrhythmias in ICD patients but negative studies are also available. These mixed findings might be attributed to differences in study design, the measure(s) used to assess psychological distress, sample size and variability in the follow-up period. In addition, stable psychological factors (e.g., personality) may modulate the influence of emotional distress on arrhythmias [36,37].

Mortality

In the past 5 years, studies that examine the impact of psychological vulnerability and distress on mortality in ICD patients have emerged. A substudy of the prospective AVID trial showed that a disease-specific quality of life measurement (Quality of Life Index – Cardiac Version [QLI-CV]) was a significant predictor of all-cause mortality, even after controlling for conventional clinical risk factors, including left ventricular function and symptomatic heart failure [39,40]. However, the mental health component score of the generic 36-item Short Form Health Survey (SF-36) was not associated with mortality. By contrast, the MADIT-II trial showed a significant association between mental health status, as assessed with the SF-12, and mortality [31]. In adjusted analyses, patients who reported psychological distress had a 39% higher risk of mortality.

Ladwig *et al.* showed that patients reporting symptoms of PTSD after ICD implantation had a threefold higher mortality risk, even after adjusting for ICD-specific factors and for affective morbidity [41]. In another study, the risk of poor prognosis was enhanced by twofold in patients with a Type D personality or patients with a high preimplantation level of ICD concerns (i.e., patient concerns about the ICD giving a shock, and irrespective of whether patients have actually received a shock) [42]. The risk of poor prognosis increased to almost fourfold in patients with clustering of both psychological risk markers compared with patients with only one or none of these markers [42].

In a recent cohort study with a long-term follow-up, the presence of depressive symptoms was shown to significantly increase the risk for all-cause mortality in ICD patients [43]. However, depression lost its predictive value when adjusting statistically for potential confounders [43]. The association between depression and mortality was investigated further by van den Broek *et al.*, with depression also being subdivided into two symptom dimensions (i.e., somatic symptoms and cognitive symptoms) [44]. Results indicated that somatic, but not cognitive, symptoms of depression predicted mortality, independent of demographic and clinical factors. Patient-reported negative, but not positive, mood was also independently related to all-cause as well as cardiac-related mortality [44]. In a recent study in patients with a CRT-D, Shalaby *et al.* found that patients with a diagnosed mood disorder were at a significantly higher risk of heart failure hospitalization or combined heart failure hospitalization and mortality, but not mortality alone [33].

Thus, the majority of available studies support an association between psychological distress and mortality in ICD patients, indicating that a subset of patients is at risk of mortality despite state-of-the-art treatment due to their psychological profile. Whether psychological factors exert an independent effect on clinical outcome in ICD patients or whether their relationship with clinical outcome can be explained by other factors that are causally related to this outcome is so far unclear.

Mechanisms linking distress to poor health outcomes

There are several plausible mechanisms that may explain the association between psychological distress and ventricular tachyarrhythmias and mortality in ICD patients. However, most of this evidence is implicit and is derived from studies that were conducted in individuals without somatic disease or in patients with general cardiovascular disease. These pathophysiological and behavioral mechanisms will be outlined in further detail below.

Autonomic nervous system dysfunction

An imbalance between the sympathetic and parasympathetic nervous systems is assumed to be one of the primary physiological mechanisms through which distress may influence overall health and predict clinical outcomes in patients with cardiovascular disease [45]. Patients with depression and anxiety tend to have impaired vagally mediated baroflex control of the heart and an increase in sympathetic tone, characterized by an increased level of norepinephrine [46], a decrease in heart rate variability [47,48]

and abnormal heart rate turbulence [49]. These parameters that reflect imbalance in autonomic tone have been implicated in the onset of cardiac events, including ventricular fibrillation, ventricular arrhythmias and mortality in ICD patients [35,43,50], and in patients postmyocardial infarction [49,51].

Heterogeneities in ventricular repolarization: QT-dispersion & T-wave alternans

Heterogeneities in ventricular repolarization, including QT-dispersion and T-wave alternans, have also been implicated in cardiovascular prognosis and SCD [45]. The QT-interval is the electrocardiographic representation of ventricular repolarization time, and variability in the QT-interval has been consistently linked with depression and emotional stress in patients with a myocardial infarction or acute coronary syndrome [52,53]. These findings could be explained by the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, which are known to exert a proarrhythmic effect attributed to cardiac and vascular sodium, potassium and calcium channel blockage and disruption of channel protein trafficking [54], thereby causing a prolongation of the QT-interval. However, findings on this topic are scarce, and in only one of the studies, the relation between QT-interval and depression remained significant even after excluding patients on antidepressants, but only among women [52].

T-wave alternans is a marker of ventricular repolarization instability that may be mechanistically related to arrhythmias [55]. One study found that T-wave alternans induced by anger in a laboratory setting predicted future ventricular arrhythmias in patients with an ICD, suggesting that distress (e.g., anger) may lead to repolarization instability [56].

Inflammation

Depression might lead to an increased activity of the hypothalamic–pituitary–adrenal axis, which results in corticotrophin hypersecretion, increased release of glucocorticoids and elevated corticotrophin-releasing hormone activation [57]. Cortisol, which is the primary glucocorticoid in humans, and corticotrophin-releasing hormone have been found to stimulate proinflammatory cytokine release, which exerts a deleterious effect on the heart due to its implication in plaque ruptures [58] and by suppressing cardiac contractility [58] while impeding cardiac remodeling [57,59]. In addition, excess cortisol can contribute to abdominal obesity, insulin resistance, hypertension, oxidative stress, altered plasma lipoprotein metabolism and vascular tone change, which can all contribute to cardiovascular disease progression [45].

Two studies found elevated levels of anxiety and PTSD to be independently associated with abnormal levels of acute-phase proteins and several proinflammatory cytokines (e.g., IL-6 and TNF-α in cardiac patients) [60]. In addition, Type D personality was associated with higher levels of proinflammatory cytokines and lower levels of anti-inflammatory cytokines in patients with heart failure [61].

Up until now, a paucity of studies have investigated the relationship between inflammatory (bio)markers and ventricular tachyarrhythmias in ICD patients. One study found no correlation between plasma levels of IL-6, TNF-α, high-sensitive C-reactive protein and brain natriuretic peptide and ventricular arrhythmic events among stable heart failure patients having ICDs, while in another study, high-sensitive C-reactive protein was correlated with ventricular tachyarrhythmias in 121 ICD recipients over a 1-year period [62,63].

Platelet activation

A few studies have found a link between depression and change in platelet activation [68], and between phobic anxiety and abnormalities in the platelet serotonin transporters and intracellular calcium levels, leading to changes in the fibrinolytic system [64]. Platelets play a key role in the development of atherosclerosis, thrombosis and acute coronary syndromes [65], thereby possibly increasing the risk for cardiac mortality in ICD patients. This effect might be attenuated by the use of SSRIs, since these have been demonstrated to reduce platelet activation by inhibiting their serotonin uptake capacity that is necessary for platelet aggregation. SSRIs may, therefore, also protect against the risk for new cardiovascular events [66]. However, it is not completely clear whether the normalization of platelet function after SSRI treatment is the result of a decrease in depressive symptoms or due to a direct effect on the platelets [67].

Behavioral mechanisms

On the behavioral side, the primary candidate mechanisms that could explain poor health outcomes in distressed ICD patients include poor medication adherence, insufficient exercise, unhealthy lifestyle habits and the cancelling of scheduled medical appointments [68,69]. Evidence suggests that patients with depression also tend to forget or skip their medication more often after adjustment for potential confounding variables, including age, ethnicity, education, social support and measures of cardiac disease severity [69], thereby increasing the risk of arrhythmias and mortality. Similarly, depression has found to be a strong determinant of all dimensions of subjective fatigue in patients with coronary artery disease [70], which may influence patient motivation to engage in exercise [70]. The lack of exercise may also result from anticipatory anxiety, with ICD patients having a restricted lifestyle because of the fear of a shock [71]. In addition, PTSD has been associated with a higher rate of physical inactivity in terms of overall exercise and self-rated level of exercise in cardiovascular patients [72]. Owing to inactivity, distressed patients may experience weight gain and be more prone to develop obesity. Weight gain and obesity can also be side effects of psychotropic drugs prescribed for affective disorders [73]. Depressed patients who have been hospitalized for cardiovascular disease are also more likely to smoke [74], with smoking probably serving as an 'emotional painkiller'. Smoking is known to cause a restriction of the arteries, modify oxygen-dependent enzymes, increase blood pressure, diminish the amount of oxygen in the body and reduce blood flow to the extremities [75]. Chemicals present in cigarettes lead to atherosclerosis and damage arteries and blood vessels, which eventually lead to cardiovascular disease, arrhythmogenic events or death [75].

Furthermore, impaired cognitive focus, reduced energy and motivation associated with depression and anxiety might affect patients' willingness to engage in self-care, to attend scheduled hospital appointments and to complete cardiac rehabilitation [76,77]. In addition, Type D personality has been associated with inadequate consultation behavior among heart failure patients (i.e., consulting a physician when experiencing cardiac symptoms), increasing the risk for adverse clinical outcomes in patients with this particular personality profile [78].

Conclusion

Cumulative evidence from large-scale prospective studies indicates that distress and psychological vulnerability may increase the risk of ventricular tachyarrhythmias and mortality in ICD patients, independent of traditional clinical risk factors and despite state-of-the-art treatment with this life-saving device. Further research is warranted to disentangle whether psychological factors constitute risk factors in their own right, whether they exert indirect effects via physiological and behavioral pathways, or whether their link with prognosis can be explained by other factors. Although it may be too premature to suggest the inclusion of psychological factors in risk algorithms, information on the psychological profile of the patient may help to optimize the management and care of this subset of vulnerable ICD patients in clinical practice.

Expert commentary

There is considerable evidence that patients implanted with an ICD may be at increased risk for ventricular tachyarrhythmias and mortality due to their preimplant psychological vulnerability or postimplant distress level, as shown in this review. The majority of this evidence comes from large-scale and well-designed prospective studies, emphasizing that the evidence is unlikely to be spurious. Moreover, the risk associated with psychological vulnerability and distress is clinically relevant, with up to a threefold increased risk, and seems to be independent of traditional risk factors, such as left ventricular dysfunction and extent of heart failure as indicated by New York Heart Association functional class [31,37,41]. Thus, despite state-of-the-art treatment with ICD therapy for the prevention of SCD, a subset of patients die prematurely due to their psychological profile and do not benefit optimally from their device. This should be placed in the context of the cost of the ICD, which is considerable, with an average price of US$25,000 for the device itself [79]. Although cost–effectiveness analyses of ICD treatment as compared with antiarrhythmic drugs showed that device therapy is cost effective [80,81], these studies did not take into account the psychological risk profile of patients.

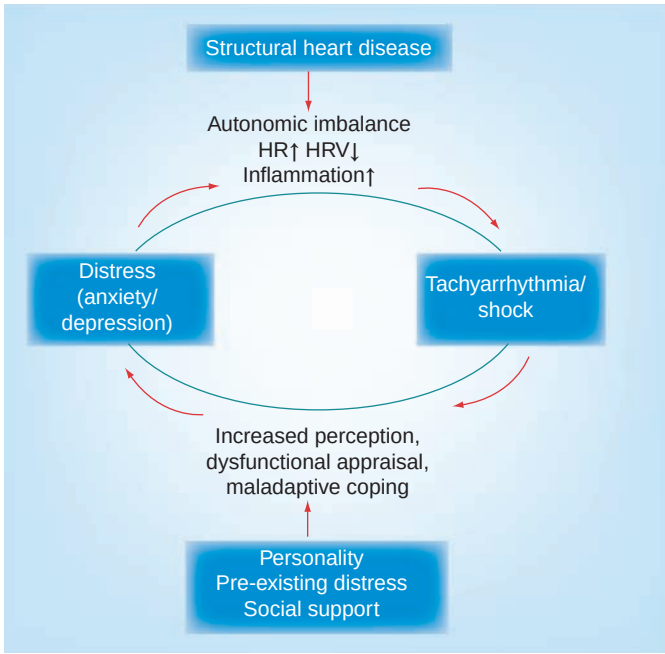

Figure 1. Supposed vicious cycle of shocks and distress.
HR: Heart rate; HRV: Heart rate variability.
Adapted from [82] with permission from Oxford University Press.

Further research in this area is warranted in order to establish whether psychological factors carry independent risk, act indirectly via physiological or behavioral pathways, or whether they can be explained by other factors. We should also explore whether psychological factors interact with demographic and clinical risk factors to enhance risk for poor clinical outcome and whether psychological factors have a place in algorithms used for risk stratification. With this knowledge, we will be better able to manage and care for the subset of ICD patients who have an increased vulnerability for adverse clinical outcomes due to their psychological profile. Until such evidence is available, we need to accept that the psychological profile of ICD patients matters in the clinical management and care and that a vicious cycle may ensue if we do not target distress in our patients irrespective of the cause (i.e., ICD shock, underlying heart disease, preimplantation psychological profile, and so on) of that distress (Figure 1) [82]. Such investment seems worthwhile given the cost of the ICD but also for the sake of the well being of our patients, as it would otherwise be tantamount to ignoring the considerable body of evidence from cardiovascular and behavioral medicine that shows that the body, mind and heart interact to influence health outcomes in cardiac patients [83].

Five-year view

Over the course of the next 5 years, if we continue to invest in the patient perspective in patients with an ICD combined with evaluating potential mechanistic pathways, we will be able to document the role of the patient's psychological profile and level of postimplant distress on clinical outcome and identify the subset of patients at the greatest risk for SCD. We will be more knowledgeable about the factors that determine the risk for SCD, whether it be due to the complex pathology underlying SCD, the psychological profile of the patient, or an interaction between several different processes and factors of a physiological, behavioral and psychological nature. Currently, there is considerable interest in the patient perspective by policy-makers, physicians and other healthcare professionals. This is also reflected in the recommendations as set out by the American Institute of Medicine for the healthcare system of the 21st century, which should be a system that provides

consistent and high-quality care that is patient-centered [84]. In these recommendations, it is stipulated that future medical treatment should fulfil the key aspects of being safe, effective, timely, equitable, efficient and patient-centered. The European Heart Rhythm Association – under the auspices of the European Society of Cardiology – also emphasizes the importance of the patient perspective in their mission statement: "The European Heart Rhythm Association mission statement is to improve the quality-of-life of the European population by reducing the impact of cardiac arrhythmias and reduce sudden cardiac death." Similarly, the device industry is investing in the patient perspective by including quality of life as an end point when designing trials and registries to evaluate the safety and efficacy of new hardware and algorithms (e.g., to reduce appropriate and inappropriate shocks).

This holds an important promise for the future wellbeing of ICD patients and is hopefully a trend that will continue. Based on these trends, it will be interesting to see how the management and clinical care of ICD patients will evolve during the next 5 years also due to changes in clinical care, with more ICD patients being followed via remote monitoring. One of the important questions will be whether the subset of ICD patients with a vulnerable pre-implant psychological profile or postimplant distress will be detected and treated in order to preserve their wellbeing and enhance their survival. Screening and monitoring of ICD patients for mental health issues is not yet part of standard clinical practice, but will hopefully be entered on equal footing with offering patients cardiac rehabilitation in the future. Current evidence from behavioral and psychological intervention trials in ICD patients indicates that we have something to offer to the subset of vulnerable ICD patients in terms of reducing their distress levels and improving their wellbeing. Even though some of these trials are plagued by methodological short comings, they show that multifactorial interventions are likely to be the most successful, including for example cognitive behavioral therapy, psycho-education about the ICD and cardiac rehabilitation as some of the mainstay components [85], which can, if warranted, be combined with pharmacological treatment. Other trials with the aim to improve mental health outcomes in ICD patients are currently underway that use comprehensive and state-of-the-art techniques in behavioral medicine, including e-health [86,87].

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Key issues

- Implantable cardioverter defibrillator (ICD) therapy is the first-line treatment for the primary and secondary prevention of sudden cardiac death, with superior survival benefits compared with antiarrhythmic drugs.
- Predicting which patients who will die suddenly from a ventricular tachyarrhythmia still remains a major challenge in clinical cardiology practice.
- The pursuit of factors that may help to enhance risk stratification has solely focused on clinical and physiological factors, despite cumulative evidence supporting a link between psychological vulnerability and the risk of ventricular tachyarrhythmias and mortality in ICD patients.
- Little is known about the pathways through which psychological factors may exert an influence on clinical outcome in ICD patients, with both plausible physiological and behavioral pathways existing.
- Further research is warranted to establish whether psychological factors comprise risk factors or risk markers that may be attributed to other factors, such as an imbalance between the sympathetic and parasympathetic nervous systems.
- It may be premature to include psychological factors in risk algorithms, but information on the psychological profile of the patient may help to optimize the management and care of this subset of vulnerable ICD patients in clinical practice.

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